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Gene drives: benefits, risks, and possible applications

Deplazes-Zemp, Anna ; Grossniklaus, Ueli ; Lefort, François ; Müller, Pie ; Romeis, Jörg ; Rügsegger, Adrian ; Schoenenberger, Nicola ; Spehn, Eva

Abstract: Gene drives are genetic elements in sexually reproducing organisms that skew the pattern of inheritance of a given characteristic. They can be used to spread a characteristic that can alter or even reduce the numbers of individuals in wild populations of a certain species. As they spread by being inherited from one generation to the next, they could persist in populations long-term. The spreading property of gene drives could be a source of great potential in areas as diverse as the control of disease vectors, invasive species, agricultural pests and predators of endangered species. However, the same property may make containment challenging and therefore may also pose novel environmental risks. The evaluation, distribution of risks and benefits and the fact that gene drives may be seen as a particularly profound interference with nature further raises novel ethical considerations.

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Gene drives: benefits, risks, and possible applications

Gene drives are genetic elements that skew the pattern of inheritance of a given characteristic in sexually reproducing organisms. They can be used to spread a characteristic that can alter or even reduce the numbers of individuals in wild populations of a certain species. As they spread by being inherited from one generation to the next, they could persist in populations long-term. The spreading property of gene drives could be a source of great potential in areas as diverse as the control of disease vectors, invasive species, agricultural pests and predators of endangered species. However, the same property may make containment challenging and therefore may also pose novel environmental risks. The evaluation, distribution of risks and benefits and the fact that gene drives may be seen as a particularly profound interference with nature raises further novel ethical considerations.

Gene drives are genetic elements that skew the patterns of inheritance, thereby accelerating the spread of a given characteristic. Over 15 to 20 generations, gene drives could spread a characteristic through an entire population, even if the characteristic, itself, is harmful to its carriers.¹ Naturally occurring DNA elements with gene drive-like properties have been known for decades.¹⁻³ However, it was the application of the CRISPR/Cas9 system⁴ that made it easier, faster and more precise to edit a genome that enabled a new generation of synthetic gene drives (Box 1). If successfully developed and applied, these types of gene drives have the potential to alter, reduce, or even – according to some researchers – eliminate a population in the environment. This novel form of population control and modification could be applied in fields as diverse as human and animal health, conservation biology, and agriculture.

So far, CRISPR-based synthetic gene drives have been developed – with varying success – in a handful of species, including fruit flies,⁵ mosquitoes,⁶⁻⁸ and yeasts.^{9,10} To date, synthetic gene drives have only been tested in the laboratory, and therefore our current knowledge of how they are expected to behave in natural systems relies primarily on theoretical models. There currently exist no immediate plans for their release into the environment.

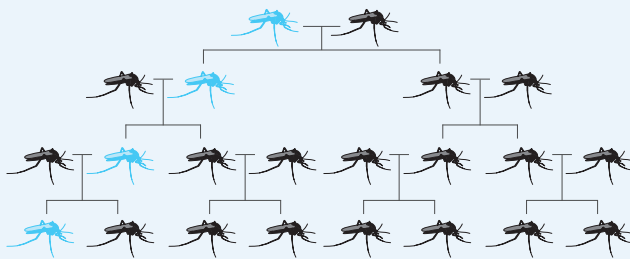
FIGURE 1

What are gene drives?

Gene drives are genetic elements that skew the pattern of inheritance of a characteristic.

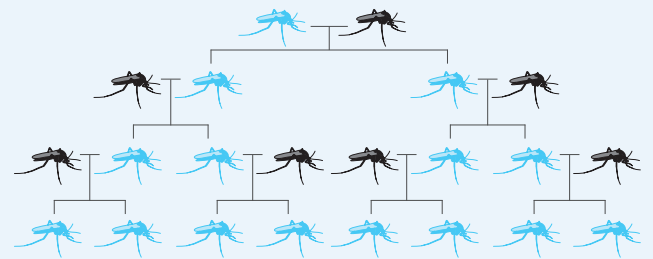
Under normal genetic inheritance

In sexually reproducing organisms, offspring have a 50:50 chance of inheriting a specific genetic variant from each parent.



Under gene drive inheritance

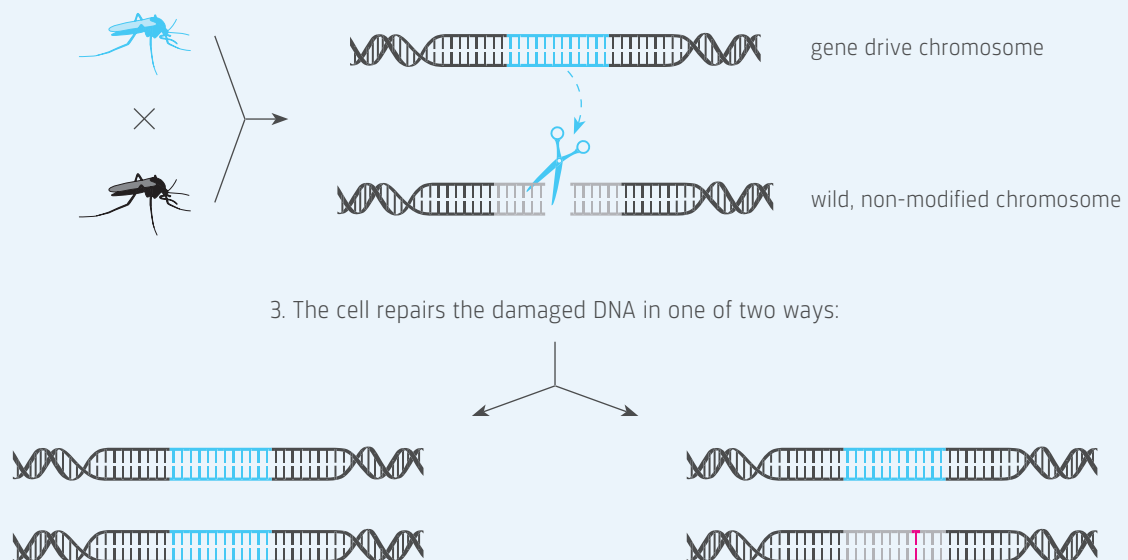
When an individual containing a gene drive mates with a wild one, nearly 100% of the offspring inherit the modified gene. As a result, within a few generations, nearly all individuals carry the gene drive and the desired characteristic, unless resistance arises.



How do CRISPR-based gene drives work?

In sexual reproduction, an individual inherits one chromosome from each parent. Therefore, when a gene drive individual mates with a wild, unmodified individual:

1. The resulting progeny inherits one chromosome with the gene drive from the gene drive parent and one non-modified chromosome from the wild-type parent.
2. The CRISPR system acts as a "molecular scissors", cutting the wild-type chromosome at the target site where the modification is to be introduced.



Outcome 1: the gene drive spreads. The gene drive-containing chromosome is used as a template and the modification is copied into the target site on the second chromosome. The cell now has two copies of the gene drive and the modification. These can act as a template for the next generation, leading to a spread of the modification in the population.

Outcome 2: the spread of the gene drive slows down over time. The ends of the two chromosome pieces rejoin, introducing small changes to the cut site. The CRISPR system may no longer recognise the target site and the gene drive element will not be copied onto the second chromosome. This may lead to "resistance" to the particular gene drive. As resistance becomes more frequent, the gene drive's spread through the population is slowed down.

What affects the spread of a gene drive?

Several factors affect the spread of the gene drive in relation to the biology of the species or the environment, such as:

- Sexual versus asexual reproduction. Gene drives only work in sexually reproducing species. Therefore, they cannot be developed for use in viruses, bacteria and some plants.¹¹
- The generation time is important in determining the spread of the gene drive. Therefore, species with short reproductive cycles, such as insects, are better suited to spread gene drives than more long-lived species, such as larger mammals.
- The evolutionary cost of the gene drive: if it affects the survival or fertility of the individual and there is also high resistance, it is less likely to spread through the population.²
- The social system of the species. Some species, e.g. rodents, live in close-knit social structures. Preferential mating with members of their social group could act as a barrier to the mating success of introduced, unrelated individuals containing the gene drive element.¹²
- Geographic barriers that may restrict the spread of gene drive elements across wider areas, e.g., restricting them to islands.¹¹

In addition, resistance is considered to be one of the major barriers to the successful spread of a gene drive.¹³ Resistance may be naturally occurring, or may arise when DNA is repaired by end-joining (Outcome 2, Figure 1). It has been observed to occur in most gene drive systems within a few generations^{6,7} with the exception of a recent lab study on *Anopheles gambiae*, the major vector of human malaria in sub-Saharan Africa.⁸ On the other hand, resistance could also act as a safeguard, making a gene drive more controllable and limiting the risk of species elimination.¹³

BOX 1

Not to be confused: genome editing and gene drives

Gene drives are sometimes confused with genome editing technology more broadly, in particular the CRISPR/Cas9 technique. **Genome editing technologies**, in general, allow the targeted modification of an organism's genome. **Synthetic gene drive systems** are just one of the many applications of genome editing. The term "synthetic" indicates that gene drives are created using gene technology methods, as opposed to naturally occurring gene drives. Whereas synthetic gene drives have only been developed in a handful of species, genome editing techniques have been successfully applied to modify the genome of a much broader range of species, such as viruses, bacteria, fungi, plants, and some animals, including humans. There are also a wider range of applications for genome editing, such as plant and animal breeding or gene therapy.

Finally, researchers are further developing ways to encode specific properties into the CRISPR-based gene drives that would limit their spread to make them safer. These include population-specific gene drives,¹¹ drives that work for a limited time period,¹⁴ drives that only spread if enough individuals carrying the gene drive are released,¹⁵ and drives that reverse the effect of an existing gene drive.¹

Self-propagating spread of gene drives: potential benefits, risks and ethical considerations

Like conventional biocontrol agents, gene drive organisms have the ability to establish themselves in the environment and spread.^{16,17} What makes this technology different is that this spreading propensity is encoded into the genetic architecture of the system. This characteristic is one of the sources of greatest potential of this technology in diverse areas, ranging from human and animal health to nature conservation and agriculture¹¹ (Figure 2). At the same time, it also raises important ethical issues, in particular because it is difficult to ensure the containment of gene drive organisms and because there are risks associated with their spread.

Potential benefits

The self-propagating nature of gene drives could result in possible benefits,¹² such as:

- Potentially higher efficiency at suppressing/altering target populations than conventional methods.
- More long-lasting than conventional methods, as the gene drive could continue to spread through multiple generations without having to be actively re-introduced.
- Greater accessibility. Due to the self-perpetuating spread intrinsic to the system, no particular infrastructure is needed to ensure spatial spread, although monitoring the effect of the intervention would be required. This means that gene drives could reach areas that are only served by limited infrastructure.
- Ease of application. The release and spread of gene drive organisms does not require a change in people's behaviour, but is a property of the system itself.
- Possibility to introduce and spread modifications specific to a species or even a population.¹¹ This could reduce undesired effects on non-target organisms compared to conventional methods such as biocides.

Potential risks

The self-propagating nature of gene drives, however, also poses specific risks, including:

- Increased challenges in containment over conventional genetically modified organisms (GMOs). This is a possible risk if gene drive organisms escape unintentionally into the environment and breed with local individuals during the research and development phase.
- Difficulties in preventing gene drive organisms from spreading into non-target populations of the same species and sexually compatible (sub-)species.¹⁸

- The risk that gene drives are difficult and perhaps impossible to stop if unexpected effects are observed during the application phase.
- The potential to spread across national borders, which could result in international regulatory incidents.

As with other interventions and technologies, there exist more general risks that are currently being discussed. These include potential negative ecological effects that are hard to predict due to the complexity of the systems and the potential for misuse.¹⁹

Ethical considerations

The idea of humans redesigning both the genome of organisms and its patterns of inheritance – with potentially irreversible consequences – may be seen by many as a particularly profound and ethically problematic interference with nature (e.g., explored in the context of synthetic biology²⁰). For others, the use of gene drives may be perceived as a continuation of the technological activities of human societies since the dawn of agriculture. Most ethical questions relate more directly to the balance of risks and benefits as well as their fair distribution amongst the stakeholders involved. Many of these considerations play a role when it comes to the implementation of regulatory and governance schemes (Box 2). For instance:

- Do we as a society first need to discuss moral acceptability issues, for example the intrinsic value of a species, prior to weighing up the risks against the opportunities?²¹
- As with other technological issues, should the technology as such or its specific applications be evaluated, assessed, discussed and regulated?
- What approaches to risk and technology assessment should be applied?
- Should the application be judged against the risks and benefits of alternative interventions as well as against the option of no intervention at all?²²
- Is a “step-by-step” risk assessment testing approach feasible, given difficulties in environmental containment and the uncertainties with respect to how gene drives will work in the wild and what impact they will have on natural systems? Could drawing from past experiences, such as the release of sterile insects or biocontrol agents, be helpful?
- Are there situations of urgency in which it is considered unjustified not to implement a gene drive solution? If so, what would those scenarios be and who should define them?²¹
- How can fair access to the technology and its applications be ensured?
- How would the risks and benefits be shared between the developers and communities that could be affected by the outcomes?
- How could we ensure that the development of a technology-based solution does not detract resources from alternative solutions?²¹

BOX 2

The legislative landscape

How gene drive research and potential release should be regulated and governed is under discussion internationally.

How are gene drives regulated in Switzerland?

Organisms with synthetic gene drives are GMOs and therefore fall under GMO legislation, both nationally (e.g., Gene Technology Act, Containment Ordinance and Release Ordinance) and internationally (in particular the United Nations Convention for Biological Diversity [CBD]).

Would research on synthetic gene drives be allowed in Switzerland?

In the lab: Yes.

According to current Swiss legislation, research with novel gene drive organisms must take place in contained laboratories, as is the case for any other novel GMO. It would not automatically be assigned into a certain risk class. Instead, the risks would be assessed for each organism and characteristic individually on the basis of defined criteria, and appropriate safety measures would be defined. Research also requires notification or authorisation under the Containment Ordinance.

In the field: Unlikely.

In Switzerland, according to the Release Ordinance (Art. 7, 1b) “The handling of genetically modified organisms in the environment must be carried out in such a manner that [...] the genetically modified organisms cannot spread or multiply in an uncontrolled way in the environment”.

Is the release of gene drives on the market allowed in Switzerland? At the moment, no.

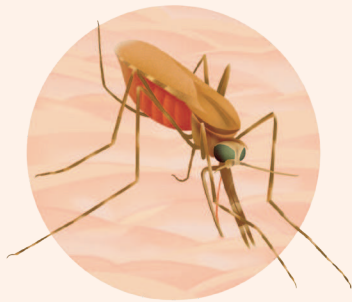
In Switzerland, a GMO can only be put into circulation after both laboratory and field trials have been conducted and an authorisation has been granted. Among others, these trials have to show that neither the GMO nor its traits can spread in an undesired way, and that it does not severely or permanently harm important ecosystem functions (Gene Technology Act Art. 6, 3).

What international regulations do gene drives come under?

Internationally, the handling, transport and safe use of GMOs is primarily regulated by the Cartagena Protocol of the CBD. It calls upon member states to protect biological diversity from adverse effects of GMOs, taking also into account risks for human health. GMOs intended to be released into the environment may only be exported into another country with the prior consent of that country. Member states are obliged to take appropriate measures to prevent the unintentional spread of GMOs across national borders. The rules on liability and redress in cases of damage are specified in a supplementary protocol. It should be noted that several countries have not signed the Cartagena Protocol, including the USA, Canada and Australia.

FIGURE 2

Possible future applications of gene drives



Human health

Approximately one out of six human diseases is transmitted by insect vectors.²³ Gene drives have been proposed as a complementary approach to insecticides and other intervention strategies to reduce disease-transmitting insects (e.g. mosquitoes, tsetse flies, ticks) and to alleviate the global burden of vector-borne diseases (e.g. malaria, Dengue, Zika and Yellow fever, Lyme disease^{6,7}).



Conservation

Gene drives have been proposed as an alternative to poisoning and live-trapping for the control of invasive species such as rodents on islands (e.g. Predator Free 2050 program in New Zealand²⁹).



Agriculture

Gene drives have been suggested as an alternative to insecticides and netting to control agricultural pests such as the rapidly expanding *Drosophila suzukii*, the spotted wing *Drosophila*,³⁰ a major threat to soft fruit production both in Switzerland and worldwide.^{31,32}

Reduction of malaria

- Malaria is caused by *Plasmodium* parasites and transmitted by female *Anopheles* mosquitoes.
- 400 000 deaths/year, mainly young children.²⁴

Current strategy and problems

- Combination of vector control (e.g. insecticide-treated bed nets, sprays) and medicines.
- Insecticide and drug resistance, limited coverage, lack of adequate health infrastructure, and costs pose a challenge to malaria eradication.²⁴

State of gene drive technology

- Natural gene drive systems (e.g. *Wolbachia* bacteria) have been previously used to control the transmission of the Dengue virus.²⁵
- Two laboratory proof-of-concepts of synthetic gene drives: i) suppressing *Anopheles gambiae*,⁷ and ii) making *A. stephensi* resistant to *Plasmodium*.⁶
- Resistance to the gene drive is a challenge; though in a recent study, resistance did not occur before the laboratory study populations collapsed entirely in 8 and 12 generations.⁸
- The Target Malaria project²⁶ works to develop, assess risks and engage local communities for a gene drive solution in Africa.

Potential benefits

- Fast acting: models predict less than five years to transform a population.²⁷
- Low cost once developed: if gene drive is efficient, there is less need for re-release.¹⁶
- Specific against a single species or population,¹¹ reducing effects on non-target insect species currently affected by non-specific insecticides; however, as malaria is often transmitted by several *Anopheles* species, targeting only one might not always effectively reduce transmission.
- Increased coverage: gene drive individuals can disperse and thus access remote areas, complementing other strategies.²⁸

Potential risks

- Unintended spill-over into other closely related *Anopheles* species.
- Strategies aiming to inhibit the *Plasmodium* parasite can be overcome if *Plasmodium* evolves resistance, potentially altering the parasite's behavior.¹⁶
- Hard-to-predict ecological effects of mosquito suppression; however, *A. gambiae* elimination is unlikely to have cascading effects on the entire ecosystem.¹²
- Potentially irreversible: once released, a gene drive could be difficult or even impossible to recall.

Other important considerations

- When is an intervention that alters, reduces, or eliminates a species morally justified?
- When could it be a matter of moral obligation to implement such a solution?²¹
- How can one effectively engage with local communities to reach a decision?
- How does the use of gene drives compare ethically to other means of population control, e.g. insecticide use?

Perspective

In Switzerland, there is currently no ongoing research on synthetic gene drives; internationally, research progresses and the possibility of controlled field trials is being discussed.³³ Drawing from previous experiences with related technologies that share some properties with gene drives, such as the release of biological control agents, sterile insect technique, transgenic insects, or *Wolbachia*-based gene drive organisms, may help us to respond to some of the future regulatory challenges of synthetic gene drives.³⁴ Due to the novelties of gene drives, a technology assessment approach that incorporates societal needs and values is crucial. As a society, we will need to consider the potential benefits, risks and

the ethical implications, including how risks and benefits are shared between the developers of the technology and the communities that are affected by the outcomes. These will depend on the species, the targeted characteristics, the intended applications, and the existence of viable alternatives. An open and transparent dialogue with all stakeholders, including researchers, industry, local communities, NGOs, governmental and international authorities, and regulatory bodies, is required to address these questions. For society as a whole, such a dialogue is essential to decide whether gene drives can and should help to solve the growing problems that we are facing in terms of human health, biodiversity, and agriculture.^{35–37}

References are included in the online version at [swiss-academies.ch/factsheets](https://www.swiss-academies.ch/factsheets)

IMPRESSUM

EDITOR AND CONTACT

Swiss Academy of Sciences (SCNAT) • Forum for Genetic Research
House of Academies • Laupenstrasse 7 • P.O. Box • 3001 Bern • Switzerland
+41 31 306 93 36 • geneticresearch@scnat.ch • [geneticresearch.scnat.ch](https://www.geneticresearch.scnat.ch)

PROJECT LEAD

Tania Jenkins • Franziska Oeschger (Forum for Genetic Research)

AUTHORS

Anna Deplazes-Zemp (University of Zurich, Forum for Genetic Research) • Ueli Grossniklaus (University of Zurich, Forum for Genetic Research) • François Lefort (Geneva School of Engineering, Architecture and Landscape) • Pie Müller (Swiss Tropical and Public Health Institute) • Jörg Romeis (Agroscope, Forum for Genetic Research) • Adrian Rügsegger (Foundation for Technology Assessment TA-SWISS) • Nicola Schoenenberger (Innovabridge Foundation, Forum Biodiversity) • Eva Spehn (Forum Biodiversity)

REVIEWERS

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